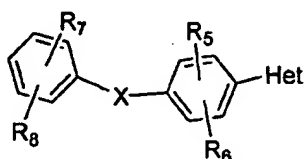


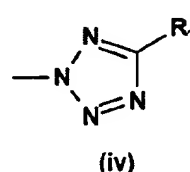
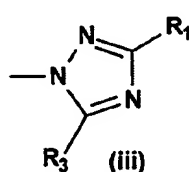
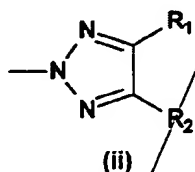
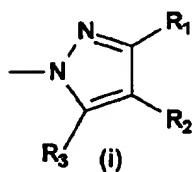
a)

- | Year | 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 | 2035 | 2036 | 2037 | 2038 | 2039 | 2040 | 2041 | 2042 | 2043 | 2044 | 2045 | 2046 | 2047 | 2048 | 2049 | 2050 | 2051 | 2052 | 2053 | 2054 | 2055 | 2056 | 2057 | 2058 | 2059 | 2060 | 2061 | 2062 | 2063 | 2064 | 2065 | 2066 | 2067 | 2068 | 2069 | 2070 | 2071 | 2072 | 2073 | 2074 | 2075 | 2076 | 2077 | 2078 | 2079 | 2080 | 2081 | 2082 | 2083 | 2084 | 2085 | 2086 | 2087 | 2088 | 2089 | 2090 | 2091 | 2092 | 2093 | 2094 | 2095 | 2096 | 2097 | 2098 | 2099 | 2100 |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| 1990 | 1991 | 1992 | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 | 2025 | 2026 | 2027 | 2028 | 2029 | 2030 | 2031 | 2032 | 2033 | 2034 | 2035 | 2036 | 2037 | 2038 | 2039 | 2040 | 2041 | 2042 | 2043 | 2044 | 2045 | 2046 | 2047 | 2048 | 2049 | 2050 | 2051 | 2052 | 2053 | 2054 | 2055 | 2056 | 2057 | 2058 | 2059 | 2060 | 2061 | 2062 | 2063 | 2064 | 2065 | 2066 | 2067 | 2068 | 2069 | 2070 | 2071 | 2072 | 2073 | 2074 | 2075 | 2076 | 2077 | 2078 | 2079 | 2080 | 2081 | 2082 | 2083 | 2084 | 2085 | 2086 | 2087 | 2088 | 2089 | 2090 | 2091 | 2092 | 2093 | 2094 | 2095 | 2096 | 2097 | 2098 | 2099 | 2100 | |



I

Het is a heteroaryl selected from the group consisting of



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R_2 and R_3 are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cyano, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfanyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, aminosulfonyl, alkylaminosulfonyl, and alkylsulfonyl;

R₅, R₆, R₇, and R₈ are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl,

aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

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R₁₀ is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR₁₁, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, heterocycle, heteroaryl, aryl, aralkyl, arylalkenyl, arylalkynyl, and cycloalkylalkylamino;

R₁₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal; and

provided that:

- 1) when Het is (ii), and X is O, then R₁₀ is not alkyl, aralkyl, aryl or OR₁₁;
- 2) when Het is (i) or (ii), then X is not NR₉;
- 3) when Het is (iii), then X is not CH₂; and
- 4) when Het is (iii), and X is O, then R₁₀ is not OR₁₁.

2. A compound of claim 1, wherein R₁ is selected from the group consisting of an alkyl optionally substituted by halogen, hydroxy, carbamoyloxy, C₁₋₆ acyl, C₁₋₆ alkylsulfonylamino, aryl, or aminocarbonyl; C(O)R₁₀; CH₂C(O)R₁₀; or SO₂R₁₀, wherein R₁₀ is selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, OR₁₁, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkenylamino, heterocycle and mono- and di-(C₁₋₆)alkylaminoalkenyl, and R₁₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal.

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3. A compound of claim 2, wherein R₁₀ is selected from the group consisting of C₁₋₆ alkyl, C₂₋₆ alkenyl, OR₁₀, amino, C₁₋₆ alkylamino, di(C₁₋₆)alkylamino, C₂₋₆ alkenylamino, di(C₁₋₆)alkylamino(C₂₋₆)alkenyl, N-morpholinyl, N-pyrrolidinyl, and N-piperazinyl.

4. A compound of claim 3, wherein R₂ and R₃ are independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl,

C₂-C₆ alkynyl, amino(C₁-C₆)alkyl, amino, C₁-C₆ alkylthio, cyano, C₁-C₆ alkylsulfinyl, hydroxy(C₁-C₆)alkyl, C₁-C₆ alkoxy, aminocarbonyl, C₁-C₆ alkylaminocarbonyl, C₆-C₁₀ arylaminocarbonyl, C₆-C₁₀ aryl(C₁-C₆)alkylaminocarbonyl, C₁-C₆ alkylcarbonylamino, C₆-C₁₀ arylcarbonylamino, and C₆-C₁₀ aryl(C₁-C₆)alkylcarbonylamino.

5. A compound of claim 3, wherein R₂ and R₃ are independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, amino(C₁-C₆)alkyl, C₁-C₆ alkylthio and aminocarbonyl.

6. A compound of claim 1, wherein R₅, R₆, R₇, and R₈ are independently selected from the group consisting of hydrogen, halo, halo(C₁-C₆)alkyl, C₁-C₆ alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, alkoxy(C₁-C₆)alkyl, nitro, amino, C₁-C₆ acylamino, amide, hydroxy, thiol, C₁-C₆ acyloxy, C₁-C₆ alkoxy, carboxy, carbonylamido and C₁-C₆ alkylthiol.

7. A compound of claim 1, wherein R₁ or R₂ is C(O)R₁₀ or SO₂R₁₀.

8. A compound of claim 7, wherein where R₁₀ is amino or C₁-C₆ alkyl.

9. A compound of claim 8, wherein X is O or S.

10. A compound of claim 9, wherein:

R₅ and R₆ are each hydrogen;

R₃ and R₄ are both H; and

R₇ and R₈ are selected from the group consisting of hydrogen, halo, halo(C₁-C₆)alkyl, C₁-C₆ alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, alkoxy(C₁-C₆)alkyl, nitro,

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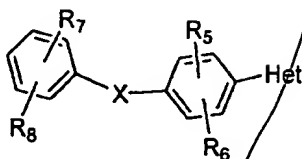
- _____**

claim

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16. A compound of Formula I:

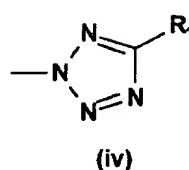
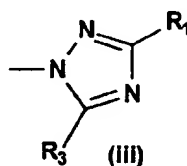
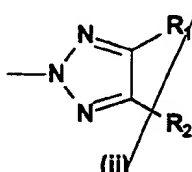
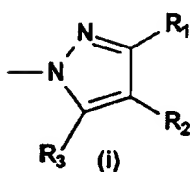


I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is a heteroaryl selected from the group consisting of



R₁ is C(O)R₁₀, CH₂C(O)R₁₀, or SO₂R₁₀ wherein R₁₀ is amino, alkyl, N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, all of which can be optionally substituted;

R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkylthio or C₁-C₆ alkylsulfinyl;

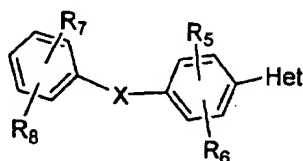
R₅, R₆, R₇ and R₈ are independently selected from the group consisting of hydrogen, halo, halo(C₁-C₆)alkyl, C₁-C₆ alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, alkoxy(C₁-C₆)alkyl, nitro, amino, C₁-C₆ acylamino, amide, hydroxy, thiol, C₁-C₆ acyloxy, C₁-C₆ alkoxy, carboxy, carbonylamido and C₁-C₆ alkylthiol;

provided that:

- 1) when Het is (ii), and X is O, then R₁₀ is not alkyl, aralkyl, aryl or OR₁₁;
- and
- 2) when Het is (iii), and X is O, then R₁₀ is not OR₁₁.

17. A pharmaceutical composition, comprising the compound of claim 1 or 16 and a pharmaceutically acceptable carrier or diluent.

18. A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I:

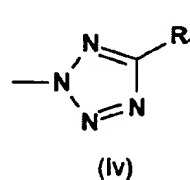
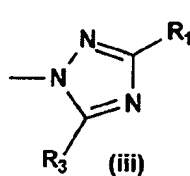
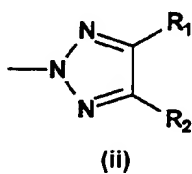
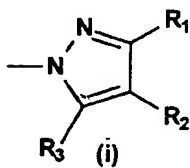


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or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is one of O, S, NR₉, CH₂, NR₉C(O), or C(O)NR₉, where R₉ is hydrogen or C₁-C₁₀ alkyl;

Het is a heteroaryl selected from the group consisting of



R₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, C(O)R₁₀, CH₂C(O)R₁₀, S(O)R₁₀, and SO₂R₁₀;

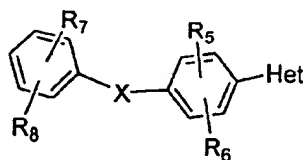
R₂ and R₃ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cyano, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, aminosulfonyl, alkylaminosulfonyl, and alkylsulfonyl;

R₅, R₆, R₇, and R₈ are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

R₁₀ is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR₁₁, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, heterocycle, heteroaryl, aryl, aralkyl, arylalkenyl, arylalkynyl, and cycloalkylalkylamino;

R₁₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkalimetal.

19. A method for treating, preventing or ameliorating neuronal loss following global and focal ischemia; treating, preventing or ameliorating neurodegenerative conditions; treating, preventing or ameliorating pain or tinnitus; treating, preventing or ameliorating manic depression; providing local anesthesia; or treating arrhythmias, or treating convulsions, comprising administering to a mammal in need of such treatment an effective amount of a compound of Formula I:

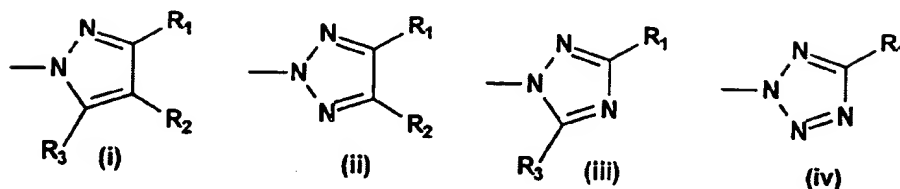


I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is one of O, S, NR₉, CH₂, NR₉C(O), or C(O)NR₉, where R₉ is hydrogen or C₁-C₁₀ alkyl;

Het is a heteroaryl selected from the group consisting of



R₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted heteroaryl, C(O)R₁₀, CH₂C(O)R₁₀, S(O)R₁₀, and SO₂R₁₀;

R₂ and R₃ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, cyano, aminoalkyl, hydroxyalkyl, alkoxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxyalkyl, alkylamino, dialkylamino, aminocarbonyl, alkylaminocarbonyl, arylaminocarbonyl, aralkylaminocarbonyl, alkylcarbonylamino, arylcarbonylamino, aralkylcarbonylamino, alkylcarbonyl, aminosulfonyl, alkylaminosulfonyl, and alkylsulfonyl;

R₅, R₆, R₇, and R₈ are independently selected from the group consisting of hydrogen, halo, haloalkyl, alkyl, alkenyl, alkynyl, hydroxyalkyl, aminoalkyl, carboxyalkyl, alkoxyalkyl, nitro, amino, ureido, cyano, acylamino, amide, hydroxy, thiol, acyloxy, azido, alkoxy, carboxy, carbonylamido and alkylthiol;

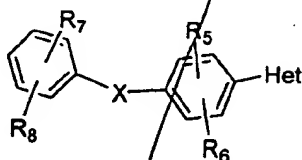
R₁₀ is selected from the group consisting of amino, alkyl, alkenyl, alkynyl, OR₁₁, alkylamino, dialkylamino, alkenylamino, dialkylaminoalkenyl, cycloalkyl, heterocycle, heteroaryl, aryl, aralkyl, arylalkenyl, arylalkynyl, and cycloalkylalkylamino;

R₁₁ is selected from the group consisting of hydrogen, optionally substituted alkyl, and an alkali metal.

20. The method of claim 19, wherein the method is for treating, preventing or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

21. A method of alleviating or preventing seizure activity in an animal subject, comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1 or 16.

22. A compound of Formula I:

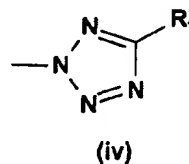
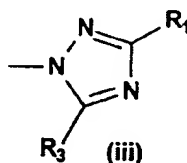
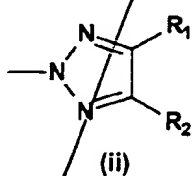
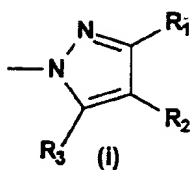


I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is a heteroaryl selected from the group consisting of



R₁ is C(O)R₁₀, wherein R₁₀ is amino, N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, all of which can be optionally substituted

R₂ and R₃ are independently hydrogen, C₁-C₆ alkyl, C₁-C₆ alkylthio or C₁-C₆ alkylsulfinyl.

R₅, R₆, R₇ and R₈ are independently selected from the group consisting of hydrogen, halo, halo(C₁-C₆)alkyl, C₁-C₆ alkyl, hydroxy(C₁-C₆)alkyl, amino(C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, alkoxy(C₁-C₆)alkyl, nitro, amino, C₁-C₆ acylamino, amide, hydroxy, thiol, C₁-C₆ acyloxy, C₁-C₆ alkoxy, carboxy, carbonylamido and C₁-C₆ alkylthiol.

23. A compound of claim 22, wherein X is O.

add
C6

add
C6